REMARKS

Reconsideration of the rejections set forth in the Office action mailed January 24, 2008 is respectfully requested. Claims 31-47 are pending in the application.

I. Amendments

Independent claims 31 and 40 have been amended to incorporate the subject matter of claims 36 and 44, respectively, without prejudice to the previous scope of these claims.

CYP3A2 has been added to the list of enzymes recited in these claims. Support is found in the specification at page 3, line 33, and in Example 3 (pages 33-36), which describes the use of antisense targeting CYP3A2 to increase the effectiveness of the drug midazolam (MZ) in mice.

To more clearly define the invention, the phrase "metabolized by a drug-metabolizing mammalian cytochrome p450 enzyme" has been moved to the preamble of claim 31, and "altering" has been changed to "improving" (see page 3, line 13 of the specification).

The phrase "by hybridizing to a target RNA molecule which encodes the enzyme" has been added to claim 31 (see specification at page 3, lines 17-18) to provide proper antecedent support for "the target RNA" in claims 33-34.

Claims 36 and 44, which are redundant in view of the amendments to the parent claims, have been replaced with claims reciting that "the morpholino antisense oligomer hybridizes to a region of the pre-mRNA that includes an exon-intron boundary", which is described as a preferred embodiment at page 19, line 30 of the specification.

No new matter is added by any of the amendments.

II. Rejections under 35 U.S.C. §112, First Paragraph

New Matter: Independent claim 31 and its dependent claims 32-39 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The new matter rejection has been addressed by the amendments noted above. Specifically, the phrase "metabolized by a drug-metabolizing mammalian cytochrome p450 enzyme" has been moved to the preamble of claim 31, and "altering" has been changed to "improving" (see page 3,

line 13 of the specification).

Written Description: Claims 31-35, 39-43 and 47 were separately rejected under 35 U.S.C. §112, first paragraph, for failing to comply with the written description requirement.

This rejection has been addressed by incorporating the subject matter of (non-rejected) claims 36 and 44 into independent claims 31 and 40. (The addition of CYP3A2 is supported by the data shown in Example 3, as noted above.) This subject matter is directed to the p450 enzymes listed on page 4 of the Office Action as being adequately described in the specification.

Enablement: Claims 31-43 and 47 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and use the invention without undue experimentation.

The Examiner found that the specification was enabling for a method of inhibiting cytochrome p450 comprising the administration of morpholino antisense oligomers targeting CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4, and for inhibiting the metabolism of drugs that are metabolized by these enzymes (pages 6-7 of Office Action).

The current claims are essentially in accordance with this scope of enablement. As noted above, independent claim 31 has been amended to recite a "method of improving the pharmacokinetics of a drug metabolized by a mammalian cytochrome p450 enzyme selected from the group consisting of CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A2 and CYP3A4 enzymes in a mammalian subject". Similarly, independent claim 40 has been amended to recite a "method of inhibiting expression of a drug-metabolizing mammalian cytochrome p450 enzyme selected from the group consisting of CYP1A1, CYP1A2, CYP2A6, CYP2B1, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A2 and CYP3A4 enzymes". The addition of CYP3A2 is supported by the data shown in Example 3, which describes the use of antisense targeting CYP3A2 to increase the effectiveness of the drug midazolam (MZ) in mice.

Although the above amendments should effectively address the current enablement rejection, applicants also note the following with respect to comments made in the Office Action. With respect to the Examiner's comments on page 8 regarding the alleged inactivity of several exemplary oligomers, applicants note that SEQ ID NO: 16 was indeed active (see page 27, lines 26-27 of the specification, which states that "Oligomer 2B1-ATG thus showed a potent in vivo antisense effect toward PB-induced CYP2B1 expression"), and SEQ ID Nos: 37 and 38 are mismatch sequences, and thus were not designed to be complementary to a p450 sequence (see page 25, lines 20-23).

With respect to the cited articles on antisense technology (Crooke, Branch, and Stein), which describe perceived problems such as unpredictable effects, difficulty in cell uptake, nonspecific binding, and irrelevant cleavage, these articles are largely irrelevant to the compounds recited in the claims. The cited articles discuss, almost exclusively, phosphorothioate-linked oligonucleotides, or, in some cases, other negatively charged-backbone oligonucleotides, such as phosphodiesters (native DNA). As stated in the applicants' specification (page 11, lines 15-21), morpholino oligomers, as recited in the claims, "have been shown to provide significantly improved selectivity in inhibiting translation of targeted sequences in comparison to phosphorothioate oligonucleotides, which are widely used in the field. The morpholino oligomers were also shown to inhibit translation at much lower concentrations than the corresponding phosphorothioates, and with little or no evidence of the substantial non-antisense activity exhibited by the phosphorothioates. See, for example, Summerton *et al.*, *Antisense & Nucleic Acid Drug Dev* **7** (2) p63-70 (1997)." The Stein article, in particular, is concerned with irrelevant cleavage caused by RNAse competent oligomers, which include phosphorothioates and phosphodiesters (page 232, column 1, first paragraph). It is not relevant to PMO oligomers, which do not activate RNAse.

In view of the foregoing, the applicants submit that the pending claims comply with the requirements of 35 U.S.C. §112, first paragraph.

III. Obviousness-Type Double Patenting Rejection

Claims 31-47 were rejected under the judicially created doctrine of obviousness-type double

patenting as being directed to an invention not patentably distinct from claims 1-20 of commonly assigned U.S. Patent No. 6,686,338.

A Terminal Disclaimer prepared in accordance with 37 CFR §1.321(b) and (c) is enclosed. The signed Terminal Disclaimer will obviate the above obviousness-type double patenting rejection.

IV. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

Respectfully submitted,

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